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The Official Action dated July 2, 2002 has been carefully considered. It is believed that the amended specification and claims submitted herewith and the following comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

In the Claims:

Applicant has cancelled claims 1-10, 13 and 16-18 due to the restriction requirement, without prejudice to Applicant's right to pursue them at a later date. For simplicity, Applicant has cancelled claims 11, 12, 14 and 15 and has submitted new claims 19-32 that are analogous to the cancelled claims.

Support for new claims 19-32 can be found in the description. Claim 19, analogous to cancelled claim 11, has been amended to delete the phrase "caused by a virus" in order to overcome the Examiner's objection. Claim 20 has been amended accordingly to specify that "the animal is infected with a hepatitis virus". New dependent claim 21 specifies that the hepatitis virus is selected from the group consisting of MHV-3 and MHV-A59. Support for claim 21 can be found throughout the application, including at page 4, lines 2-5, page 25, line 7 to page 27, line 17 and page 31, line 18 to page 34, and the Examiner has acknowledged that there is support for the method as it relates to murine hepatitis viruses. New dependent claims 22-30 specifically refer to the nucleotide sequences being complemented, in particular, nucleotide sequences found in SEQ ID No. 1. Support for these claims can be found throughout the application, in particular in Figure 2 and SEQ ID No 1 and at page 6, lines 5-11 and page 28, lines 4-13. These references to sequences overcome Examiner's objection that the sequences were not defined and it was not

clear where the preferred sequence starts or ends. New claim 31 and 32 are analogous to cancelled claim 15.

37 CFR 1.67(a)

The Examiner has objected that the declaration is defective for a number of reasons. The Examiner informed Applicant in a telephone conversation on September 23, 2002 that, due to a clerical error at the United States Patent and Trademark Office, the Patent Office file did not contain the application data sheet that Applicant filed with the declaration at the time of entry into the national phase in the United States. Applicant resubmits herewith the declaration and application data sheet first filed on August 24, 2001, together with a copy of the stamped card evidencing receipt by the U.S.P.T.O. of the declaration and application data sheet on that date. As the Examiner's objections are now moot, Applicant requests that the objections to the declaration be withdrawn.

37 CFR 1.821 – 1.825

The Examiner has objected that the application contains nucleotide sequence disclosures but does not comply with the requirements of 37 CFR 1.821-1.825, and that the specification and claims do not contain proper sequence identifiers. In response, Applicant submits herewith (1) a copy of the Notice to Comply; (2) a Sequence Listing in paper form; (3) a Sequence Listing in computer readable form (a 3.5" floppy diskette) in the ASCII format and (4) a statement (set forth below) that the paper form and the computer readable form of the Sequence Listing are the same.

In accordance with the requirements of 37 CFR 1.821-1.825 the undersigned verifies that the paper form of the Sequence Listing and the computer readable form of the Sequence Listing are the same.

The application has herein been amended at pages 4, 21-24 and 29 to append SEQ ID Nos. and to incorporate a Sequence Listing. The Sequence Listing has been incorporated into the specification at pages 46 to 51 and includes SEQ ID Nos. 1 to 18, which are sequences in the specification as filed but were not included in a Sequence Listing. Support for SEQ ID No. 1 can be found in Figure 2, support for SEQ ID Nos. 2-12 can be found on pages 22-23, and support for SEQ ID Nos. 13-18 can be found on page 29 of the application as filed. We confirm that the substitute specification does not contain any new matter. In view of the foregoing, it is requested that the Examiner withdraw the objections to the application based on sequence requirements.

35 USC § 112, second paragraph

The Examiner has objected to claims 11, 12, 14 and 15 under 35 USC § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant has amended claim 11 (new claim 19) without prejudice to remove the reference to "caused by a virus" objected to by the Examiner and made a consequential amendment to new claim 20 necessitated by the amendment to claim 19. Claim 14 has been deleted, and replaced with claims 22-30 that contain specific references to SEQ ID No 1. As such, Applicant requests that the objections to claims 11, 12, 14 and 15 on these bases be withdrawn. With regard to the other Examiner's objections under 35 USC § 112, second paragraph, Applicant respectfully submits the following arguments to traverse the objections.

The Examiner asserts that "Claim 11 is unclear because it cannot be determined how immune coagulation caused by a virus is distinguished from immune coagulation caused by something else, such as endotoxin shock and cancer." Applicant has amended claim 11 (new claim 19) to remove the words "caused by a virus", rendering

the claim sufficiently definite and Examiner's objection moot. There is support in the description at page 4, lines 6-14 for the amended claim. Dependent claim 20 has been amended accordingly to specify that "the animal is infected with a hepatitis virus". Support for this amendment can be found throughout the application, for example, from page 3, line 8 to page 4, line 14.

As mentioned above, claim 14 has been deleted and replaced with claims 22-30.

The Examiner has also objected that "claims 14 and 15 are vague and indefinite because it cannot be determined what is being complemented." It is respectfully submitted that the present claims are method claims, and not claims to specific gene or oligonucleotide sequences. As described in further detail below under the heading "Written Description", Applicant has defined the method of the invention in sufficient detail to permit a person skilled in the art to carry it out, and it should not be necessary for Applicant to set out particular oligonucleotide sequences. Furthermore, Applicant has provided herewith new claims 22-30 that contain specific references to the nucleotide sequences being complemented, in particular, nucleotide sequences found in SEQ ID No. 1.

In view of the foregoing, Applicant respectfully requests that the objections to claims 11, 12, 14 and 15 under 35 USC §112, second paragraph be withdrawn.

35 USC § 112, first paragraph

(a) Written Description

The Examiner has objected to claims 11, 12, 14 and 15 under 35 USC § 112, first paragraph as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the

inventor had possession of the claimed invention. Applicant respectfully disagrees with the Examiner for the reasons that follow.

In order to satisfy the written description requirements the application must contain a written description of the claimed invention that enables a person skilled in the art to practice the invention. In the present case, claims 11, 12, 14 and 15 (and new claims 19-32) are directed to a method of preventing or reducing immune coagulation comprising administering an effective amount of an inhibitor of LF-A1 gene or protein. Applicant is not attempting to claim the LF-A1 gene or protein or particular fragments thereof *per se*. The Examiner asserts that "it cannot be determined which strand the antisense oligonucleotide is complementing or how many (antisense) oligonucleotides are being claimed". The Examiner further states that the exact sequence of the oligonucleotide is not defined by the complementary region recited in the application, and that there is no teaching for how one skilled in the art would structurally identify any other antisense oligonucleotide, relying on the decision in University of California v. Eli Lilly, 119 F.3d at 1568, 43 USPQ 2d 1398 at 1406 (CAFC 1997). As the Examiner is aware, the Eli Lilly decision dealt with whether or not the disclosure of a rat sequence was sufficient written description for a claim that related to the sequence from all vertebrates. As a result, the case dealt with the claims that related to nucleic acid molecules *per se* and not to new uses of nucleic acids or proteins. Applicant respectfully submits that the Examiner is applying the decision in the present case to method claims using the principles that were established when examining claims to novel nucleic acid or protein sequences. Further, in the Revised Interim Written Description Guidelines Training Materials (which were designed to aid PTO patent examiners in applying the Written Description Guidelines and assist patent applicants in responding to the PTO when written description issues are raised) there is only one example, Example 18, that addresses the case wherein the invention relates to a method where the novelty is in the method steps and not in the

nucleic acid molecule. In that case, the example determines that "a single embodiment is representative of the genus".

In the present case, there is more than ample written description to support the claims. In particular, the claims are drawn to a method of preventing or reducing immune coagulation comprising administering an effective amount of an inhibitor of LF-A1 gene or protein. In other words, the invention lies in the determination that inhibition of LF-A1 can block fgl2 induction and prevent or reduce immune coagulation and the application contains sufficient detail to convey that Applicant was in possession of the claimed invention. Further, the Examiner has acknowledged that an embodiment of the invention can be found in the specification. Applicant submits that in light of the Applicant's invention, a person skilled in the art would be able to identify suitable inhibitors and antisense oligonucleotides for use in the method of the present invention.

In view of the foregoing, Applicant respectfully submits that the disclosure of the application is sufficient in order to meet the Written Description Guidelines. Consequently, the Applicant respectfully requests that the objections to claims 11, 12, 14 and 15 under 35 USC §112, first paragraph be withdrawn.

(b) Enablement

The Examiner has further objected to claims 11, 12, 14 and 15 under 35 USC §112, first paragraph as not being enabling for preventing or reducing immune coagulation caused by any virus by administering any inhibitor of a LF-A1 gene or protein. Applicant respectfully disagrees with the Examiner for the reasons that follow.

As stated previously, the claims relate to a method of preventing or reducing immune coagulation comprising administering an effective amount of an inhibitor of LF-A1

gene or protein. The claims are not directed to the LF-A1 gene or protein or particular fragments thereof *per se*. Consequently, after having read the present application one skilled in the art would understand that by inhibiting LF-A1 one can prevent or reduce immune coagulation that is associated with fgl2 expression and could readily isolate antisense oligonucleotides that would be useful in the present invention. Since the LF-A1 gene and fgl2 promoter sequences for both mouse and human were known in the art, a person skilled in the art upon reading the present application would be able to construct the antisense oligonucleotides required.

Finally, the Examiner's objection that "there is no indication that administering the instant oligonucleotide would not cause detrimental effects on normal immune system functioning" is without merit. It is sufficient that the method of the present invention can effectively inhibit an LF-A1 gene or protein and prevent or reduce immune coagulation; a determination of whether or not other immune functions would be affected is irrelevant to patentability.

In view of the foregoing, Applicant respectfully requests that the objections to claims 11, 12, 14 and 15 under 35 USC §112, first paragraph be withdrawn.

35 USC § 103(a)

The Examiner has objected to claims 11, 12, 14 and 15 under 35 USC § 103(a) as being unpatentable over Ding et al. (J. Virology, 71(12): 9223-9230, 1997), in view of Mizutani et al. (J. Veterinary Medical Science, 56(2): 211-215, 1994). Applicant respectfully disagrees with the Examiner for the reasons that follow.

Ding et al. teaches that the fgl2 gene and protein are selectively expressed in response to murine hepatitis virus strain 3 (MHV-3) infection. Examiner notes that

Ding et al. does not teach reducing immune coagulation with an antisense oligonucleotide that complements the promoter of the fgl2 gene. Furthermore, claims 11, 12, 14 and 15 presently under consideration (and new claims 19-32) are directed to preventing or reducing immune coagulation by inhibiting the LF-A1 gene or protein. The present inventor has found that liver factor A1 (LF-A1) protein binds to a CIS-acting regulatory element, LF-A1 binding element, that is found upstream of the fgl2 coding region. Ding et al. does not disclose any information about inhibiting the LF-A1 gene or protein in order to prevent or reduce immune coagulation.

The deficiencies in Ding et al. are not remedied by Mizutani et al. Mizutani et al. teaches that cell lines which express either sense or antisense RNA that is directed against the nucleocapsid protein gene of MHV reduces MHV-specific RNA synthesis and viral replication. This is a different target from that of the present invention. Mizutani et al. does not disclose the role of LF-A1 in fgl2 induction. Examiner states that "one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because Ding et al. teaches that the induction of fgl-2 RNA transcripts promotes immune coagulation and Mizutani et al. teaches inhibition of viral transcription with an antisense oligonucleotide." In fact, one of ordinary skill in the art would not have been able to produce the claimed invention, given that the role of LF-A1 was not yet known.

In view of the foregoing, one skilled in the art having read Ding et al. in combination with Mizutani et al. would not have been motivated to inhibit the LF-A1 gene or protein in order to prevent or reduce immune coagulation, because no such role for the LF-A1 gene and protein was known at the time. Consequently, it is respectfully requested that the objections to the claims under 35 USC §103(a) be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification, claims and abstract by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE".

In view of the foregoing, Applicant submits that the application is in order for allowance and early indication of that effect is respectfully requested. Should the Examiner deem it beneficial to discuss the application in greater detail, she is kindly requested to contact Anita Nador by telephone at (416) 957-1684 at her convenience.

Respectfully Submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In th Specification:

Sequence Listing pages 46-51 have been inserted into the specification.

Paragraph beginning at page 4, line 23 has been amended as follows:

--The invention will now be described in relation to the drawings in which:

Figure 1 is a schematic representation of the oligonucleotide maps of the recombinant viruses.

Figure 2 (SEQ.ID.NO: 1) is a schematic and nucleic acid sequence of the fgl2 gene.

Figures 3A and 3B are bar graphs showing induction of fgl2 in the presence of various viruses.--

Paragraphs beginning at page 21, line 22 to page 24, line 4 have been amended as follows:

--Expression of fgl2 was detected by RT-PCR. Freshly isolated macrophages, at a multiplicity of infection (MOI) of 2.5, were infected with different strains of viruses for 6 hours. 1x 107 macrophages were pelleted in 1.5 ml Eppendorf tube and total cellular RNA was isolated by 8M acid-guanidium hydrochloride extraction in a modified procedure as previously described (Evans and Kamdar, 1990). The quantity and quality of RNA was examined by spectrophotometry and on a 1% analytical agarose gel containing formaldehyde. RNA (5mg) was reverse transcribed using Moloney Murine Leukemia Virus Reverse Transcriptase (M-MLVRT) in 20 ml reactions, as recommended by manufacturer. PCR was then performed in 50 ml reactions using 1ml portion of cDNA and the primers fgl2-318 (TGC CCA CGC TGA CCA TCC A) (SEQ.ID.NO: 2) corresponding to nucleotide 318 ñ 336 of Balb/c fgl2

cDNA (M 15761) and FGL2-1224 (GAG ACA ACG ATC GGT ACC CCT) (SEQ.ID.NO: 3) corresponding to nucleotides 1224 -1244 of Balb/c fgl2 cDNA. (M16238), which yield a 906 bp band in 1% agarose DNA gel. Amplification products were not obtained when reverse transcriptase was omitted (data not shown). RT-PCR for GAPDH was also set up as an internal control to assess the quality of first strand synthesis.

Creation of N gene and fgl2 promoter constructs

Restriction enzymes used to create constructs were obtained from GIBCO BRL, Life Technologies, USA. All plasmids were purified using Qiagen Maxiprep Kits, and grown in DH5 E. coli bacteria (GIBCO BRL).

MHV-2 and A59 are different sizes. The entire N gene coding regions and 3' UTRs of MHV-A59, MHV-2, ML3 and ML11 were amplified by RT-PCR. RNA was originally extracted from infected macrophages. The sense primer ACG ATG TCT TTT GTT CCT GGG (SEQ.ID.NO: 4) was phosphorylated chemically at position 1 to achieve directed insertion and ligation of PCR products to its vector; the anti sense primer at position 1654 TTT TTT TTT GTG ATT CTT CCA (SEQ.ID.NO: 5) had a poly T group to match the poly A tail at the 3' end of nucleocapsid genomic RNA. The N gene fragments were subcloned into the 5.0 Kb expression vector pCR 3.1 (Invitrogen), under the control of the CMV promoter and bovine growth hormone 3'-processing signals. External restriction endonuclease Hind III and Pst I and internal restriction endonuclease Eco RI, Eco RV were used to analysis the size and orientation of N gene insert in recombinant plasmid constructs.

Luciferase Reporter Constructs: A 1.3 kb DNA fragment flanking the 5' end of mouse fgl2 was released by restriction digestion with EcoRV and Sal I from a subclone pBluescript-m166 (pm166) of mouse genomic P1 plasmid (Genome System Inc.) which contains the entire mouse fgl2 gene. This fragment was sequenced by cycle sequencing on an automated DNA sequencer (Model 377, Applied Biosystems) using dideoxy dye terminator chemistry. This sequence has

been deposited into Genbank with the Accession number AF025817 (Figure 2) (Koyama et al., 1987). This 1.3 kb fragment was inserted into Sma I and Xho I sites of the pGL2-basic luciferase reporter vector (Promega) to form pfgl2(-1328)LUC. 5' deletion constructs of fgl2 promoter were made by first amplifying the specific fragment using pm166 as template and then cloned into PCR 2.1 cloning vector (Stratagene) and resubcloned into pGL2-basic plasmid at Xho I and Hind III sites. The reverse primer (GCC ACA ACC AAC CAG GAA G) (SEQ.ID.NO: 6) was used to make all deletion constructs by PCR amplification. The upstream primers used were: GAG CTG AGT GAT GGG GAA GGA (SEQ.ID.NO: 7) for pfgl2(-693)LUC, CCA CTG ACG ATT ACA TAG CC (SEQ.ID.NO: 8) for pfgl2(-625)LUC, GGA CCT TTG TTC TGA TTA GGG GC (SEQ.ID.NO: 9) for pfgl2(-511)LUC, CGC AGA CAT TTA GAC GTT CC (SEQ.ID.NO: 10) for pfgl2(-372)LUC, and GGG CAC TGG TAT TAC AAC TGT (SEQ.ID.NO: 11) for pfgl2(-306)LUC. All promoter-luciferase report constructs were sequenced to confirm the orientation and to verify the sequence. Positive control, pGL2 Control plasmid with SV-40 promoter, and RSV b-gal vector were from Promega. A 2Kb tissue factor promoter construct pTF(-2Kb)LUC was a kind gift of Dr. Nigel Mackman (Mackman et al., 1990).

N gene Sequence of different virus strains

The N gene sequence of multiple clones for each strain of virus was determined using primer-directed strategies by cycle sequencing on an automated DNA sequencer, using the ABI PRISMTM dRhodamine Terminator Cycle Sequencing Reading Reaction Kit (Model 377, PE Applied Biosystems). The T7 primer and pCR3.1 reverse primer were used for 5' to 3' and 3' to 5' sequence, respectively. A new primer CTC AGG GCT TTT ATG TTG AAG (SEQ.ID.NO: 12) (MHV-ND557) at position 557 was also designed based on the outcome of sequencing and the published cDNA sequence of MHV-A59 to complete the sequencing. Extension products were purified by ethanol/sodium acetate precipitation. Samples were

subjected to electrophoresis on the ABI PRISM 310. The sequence was analyzed using the DNAsis for windows, sequence analysis software (Hitachi Software Engineering America Ltd, San Bruno, CA, USA).--

Paragraph beginning at page 29, line 5 has been amended as follows:

--For the LF-A1 site (-338/-319 of fgl-2 promoter region):

5'-CAC TAG TGG ACC AAG TAT-3' (SEQ.ID.NO: 13) AND 5'- AAT TAT ACT TGG TCC ACT AGT G-3' (SEQ.ID.NO: 14);

For the IE1.2 SITE (-353/-336 of fgl2 promoter region)):

5'-TTC CAA CTC TTT CCC AC-3' (SEQ.ID.NO: 15) AND 5'-AAT TGT GGG AAA GAG TTG CAA (SEQ.ID.NO: 16);

For the GMCSF site (-368/-351 of fgl2 promoter region):

5'-ACA GAC ATT TAG AGG TTC-3' (SEQ.ID.NO: 17) AND 5'-AAT TGA ACG TCT AAT GTC TGT-3' (SEQ.ID.NO: 18)--

In the Claims:

New claims 19-32 have been submitted as follows.

19. (New) A method of preventing or reducing immune coagulation associated with fgl2 expression comprising administering an effective amount of an inhibitor of LF-A1 gene or protein to an animal in need thereof.

20. (New) The method according to claim 19 wherein the animal is infected with a hepatitis virus.

21. (New) The method of claim 20 wherein the hepatitis virus is selected from the group consisting of MHV-3 and MHV-A59.

22. (New) The method according to claim 19 wherein the inhibitor inhibits the LF-A1 protein and is an antisense oligonucleotide sequence that comprises a sequence complementary to the fgl-2 promoter region of the animal or a portion of said fgl-2 promoter region effective in inhibiting LF-A1 binding to the LF-A1 binding element of the promoter region of fgl-2.

23. (New) The method according to claim 22 wherein the oligonucleotide sequence comprises at least 8 nucleotides that is complementary to an 8 nucleotide consecutive sequence of the fgl-2 promoter region.

24. (New) The method according to claim 22 wherein the fgl-2 promoter region comprises the nucleotide sequence 957 to 1023 of SEQ. ID. NO. 1 and the LF-A1 binding element comprises the nucleotide sequence 997 to 1004 of SEQ. ID. NO. 1.

25. (New) The method of claim 24 wherein the oligonucleotide sequence comprises a sequence that is complementary to the LF-A1 binding element of the fgl-2 promoter region.

26. (New) The method according to claim 22 wherein the inhibitor consists of an oligonucleotide sequence complementary to the fgl-2 promoter region of the animal.

27. (New) The method according to claim 26 wherein the oligonucleotide sequence complementary to the fgl-2 promoter region of the animal is complementary to the nucleotide sequence 957 to 1023 of SEQ. ID. NO. 1.

28. (New) The method according to claim 22 wherein the oligonucleotide sequence consists of 8 nucleotides that is complementary to an 8 nucleotide consecutive sequence selected from the nucleotide sequence 957 to 1023 of SEQ. ID. NO. 1.

29. (New) The method according to claim 22 wherein the oligonucleotide sequence consists of a sequence that is complementary to the LF-A1 binding element of the promoter region of the fgl-2 gene.

30. (New) The method according to claim 29, wherein the LF-A1 binding element of the fgl-2 promoter region is nucleotide sequence 997 to 1004 of SEQ. ID. NO. 1.

31. (New) The method of claim 19 wherein the inhibitor is an inhibitor of the LF-A1 gene.

32. (New) The method of claim 31 wherein the inhibitor is an antisense oligonucleotide sequence comprising a sequence complementary to a nucleic acid sequence from the LF-A1 gene.

Please replace claim pages 46-48 currently of record with the above new claims 19-32 as claim pages 52-53.

In the Abstract:

Please renumber the abstract page currently of record as abstract page 54.